Echocardiography does not predict mortality in hemodynamically stable elderly patients with acute pulmonary embolism

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Running headline: Echocardiography in pulmonary embolism

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ABSTRACT

Background: The evidence on the prognostic value of transthoracic echocardiography (TTE) in elderly, hemodynamically stable patients with pulmonary embolism (PE) is limited.

Objectives: To evaluate the prevalence of common echocardiographic signs of right ventricular (RV) dysfunction and their prognostic impact in hemodynamically stable patients aged ≥65 years with acute PE in a prospective multicenter cohort.

Methods: TTE was performed by cardiologists. We defined RV dysfunction as a RV/left ventricular ratio >0.9 or RV hypokinesis (primary definition) or the presence of ≥1 or ≥2 of 6 predefined echocardiographic signs (secondary definitions). Outcomes were overall mortality and mortality/non-fatal recurrent venous thromboembolism (VTE) at 30 days, adjusting for the Pulmonary Embolism Severity Index risk score and highly sensitive troponin T values.

Results: Of 400 patients, 36% had RV dysfunction based on our primary definition, and 81% (≥1 sign) and 53% (≥2 signs) based on our secondary definitions, respectively. Using our primary definition, there was no association between RV dysfunction and mortality (adjusted HR 0.90, 95% CI 0.31-2.58) and mortality/non-fatal VTE (adjusted HR 1.09, 95% CI 0.40-2.98). Similarly, there was no statistically significant association between the presence of ≥1 or ≥2 echocardiographic signs (secondary definitions) and clinical outcomes.

Conclusion: The prevalence of echocardiographic RV dysfunction varied widely depending upon the definition used. There was no association between RV dysfunction and clinical outcomes. Thus, TTE may not be suitable as a stand-alone risk assessment tool in elderly patients with acute PE.

Clinical Trial Registration: http://clinicaltrials.gov. Identifier: NCT00973596.

Keywords: echocardiography, pulmonary embolism, mortality

INTRODUCTION

Evidence suggests that echocardiographic signs of right ventricular (RV) dysfunction or pulmonary hypertension (hereafter called signs of RV dysfunction) are associated with a 2-fold increase in short-term overall mortality in hemodynamically stable patients with acute pulmonary embolism (PE) [1, 2]. Several professional societies have therefore incorporated transthoracic echocardiography (TTE), alone or in combination with cardiac biomarkers, into their risk assessment strategies for hemodynamically stable patients with acute PE [3, 4]. According to current recommendations, fibrinolysis may be considered in selected hemodynamically stable patients with RV dysfunction [3, 4]. TTE has been widely adopted into clinical practice and despite its costs and the need for a trained physician, currently more than a third of patients diagnosed with acute PE undergo TTE [5, 6].

Although elderly patients have more severe venous thromboembolism (VTE) and a higher short-term mortality rate than younger patients [7, 8], the prognostic performance of TTE to predict mortality has not been specifically examined in elderly patients with acute PE. The aim of this study was to prospectively evaluate the prevalence of common echocardiographic signs of RV dysfunction and their prognostic impact in elderly patients with acute PE.

METHODS

Cohort sample

This study was conducted between September 2009 and June 2012 as part of a prospective, multicenter cohort study to assess long-term medical outcomes and quality of life in patients aged ≥65 years with an acute VTE from all five Swiss university and four high-volume non-university hospitals [9]. Consecutive patients aged ≥65 years with an acute VTE were identified in the inpatient and outpatient services of all participating study sites. Exclusion criteria were catheter-related thrombosis, insufficient German or French-speaking ability, no follow-up possible (i.e., terminal illness), an inability to provide informed consent (i.e., severe dementia), or previous enrollment in the cohort. The study was approved by the Institutional Review Board at each participating center. The detailed study methods were previously published [9]. For the present study, we only considered hemodynamically stable patients with an acute symptomatic, objectively confirmed PE [9]. Hemodynamic stability was defined as a systolic blood pressure of ≥90 mm Hg at the time of PE diagnosis.

Baseline data collection

Trained study nurses prospectively collected baseline demographic characteristics, comorbid conditions, type of PE (unprovoked vs. provoked), localization of PE, vital signs, routine laboratory findings (hemoglobin, serum creatinine), and anticoagulation-related treatments. In addition, we recorded whether the patient was admitted to the intensive care unit or received intravenous catecholamines, cardiopulmonary resuscitation, vena cava filter, fibrinolysis, or thromboembolectomy in the hospital.

We also collected venous blood samples at the time of PE diagnosis. Samples were immediately centrifuged, frozen, and stored at -80°C and sent for analyses to a core laboratory. Plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and highly sensitive troponin T (hsTnT) were measured quantitatively using a Cobas e601 automated immunoanalyser (electrochemiluminescence methods, Hoffmann-La Roche, Rotkreuz, Switzerland).

Echocardiographic examination

Patients underwent TTE at the time of study enrollment to assess RV function. All TTEs were performed by on-site cardiologists according to a standardized protocol. The cardiologists were blinded to patients' baseline characteristics and treatments. The following six signs of RV dysfunction/pulmonary hypertension were recorded: 1) RV/LV end-diastolic diameter ratio >0.9 in the apical four chamber view, 2) RV hypokinesis (defined as a moderately or severely abnormal motion of RV free wall), 3) paradoxical septal motion, 4) decreased or absent inspiratory collapse of the inferior vena cava, 5) shortened pulmonary acceleration time in the parasternal short axis view (≤100 ms), and 6) increase in RV/right atrial gradient in the apical four chamber or parasternal short axis view (≥30 mm Hg) [10-14]. For the present analysis, we considered only patients who had TTE within three days of PE diagnosis [15].

We used the presence of a RV/LV ratio >0.9 or RV hypokinesis as our primary definition of RV dysfunction, as suggested by the American Heart Association [3]. However, because the definition of RV dysfunction varies widely across studies, we also defined RV dysfunction as the presence of at least one and at least two of six echocardiographic signs described above, respectively (secondary definitions).

Study outcomes

The primary outcome was overall mortality within 30 days of PE diagnosis. The secondary outcome was overall mortality/non-fatal recurrent VTE at 30 days. Recurrent VTE was defined as symptomatic, objectively confirmed recurrent PE or a new symptomatic deep vein thrombosis [9]. Follow-up included a face-to-face patient interview and hospital chart review at 90 days, complemented by proxy interviews and an interview of the patient's primary care physician. A committee of three blinded clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to PE, possibly due to PE, or due to another cause [9]. Final classifications were made on the basis of the full consensus of this committee.

Statistical analysis

We compared baseline characteristics and descriptive outcome data of patients with and without RV dysfunction using the Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous variables as appropriate. In patients treated with vitamin K antagonists, we compared the percentage of time spent in the therapeutic INR range (2.0-3.0) using analysis of variance [16]. We used Kaplan-Meier curves and the log-rank test to compare the cumulative overall mortality and overall mortality/recurrence of non-fatal VTE within 30 days in patients with and without RV dysfunction.

We examined the association between RV dysfunction and clinical outcomes using a Cox-regression model. We adjusted all models for the Pulmonary Embolism Severity Index risk score and hsTnT. The Pulmonary Embolism Severity Index is a validated prognostic score and comprises 11 clinical variables, including demographics (age, gender), comorbid diseases (cancer, heart failure, and chronic lung disease), and vital signs (altered mental status, pulse, systolic blood pressure,

respiratory rate, arterial oxygen saturation, and temperature) [17]. Given that NT-proBNP is another marker for RV dysfunction, we did not adjust for this parameter [18]. Because RV dysfunction may be transitory, we also examined the association between RV dysfunction and clinical outcomes in the subgroup of patients who had TTE within one day of PE diagnosis [19]. Missing values in covariates used for adjustment were assumed as normal. We considered *P*-values <0.05 to be statistically significant. All analyses were performed using Stata 14.0.

RESULTS

Study sample

Overall, 685 hemodynamically stable patients with PE were initially enrolled in our study. After exclusion of 285 (42%) patients (277 had no TTE within three days and 8 withdrew consent early or did not allow use of their data), our final sample comprised 400 patients. Excluded patients were more likely to be women (53% vs. 44%, *P*=0.02) and to have hospital-acquired PE (22% vs. 14%, *P*=0.007) or anemia (43% vs. 35%, *P*=0.029) than analyzed patients. The other baseline characteristics, including illness severity based on the Pulmonary Embolism Severity Index, were comparable. There were no differences in mortality, intensive care admission, catecholamine use, fibrinolysis, cardiopulmonary resuscitation, or thromboembolectomy (data not shown).

Patients with RV dysfunction based on our primary definition were older and were more likely to have a history of VTE, unprovoked, central, or lobar PE, a heart rate ≥110/minute, a respiratory rate ≥30/minute, and an arterial oxygen saturation <90% than patients without RV dysfunction (Table 1). Patients with RV dysfunction had also a higher proportion of NT-proBNP >500 pg/ml, and were more likely to be admitted to the intensive care unit, receive fibrinolysis, and have cardiopulmonary resuscitation than patients without RV dysfunction. In patients treated with vitamin K antagonists, the percentage of time in the therapeutic range did not vary between patients with and without RV dysfunction (61% vs. 63%, *P*=0.37).

The prevalence of echocardiographic signs of RV dysfunction varied from 15% for RV hypokinesis to 54% for pulmonary acceleration time ≤100 ms (Table 2). Overall, 36% of patients had a RV/LV end-diastolic diameter ratio >0.9 or RV hypokinesis (primary definition), and 81% and 53% had ≥1 and ≥2 signs of RV dysfunction, respectively (secondary definitions).

Comparison of outcomes

Fifteen patients (3.8%) died within 30 days of the index PE. Of these, 5 died from definite/possible PE, 3 from cancer, 1 from left ventricular heart failure, 1 from other pulmonary causes, 2 from bleeding, 2 from sepsis, and 1 from an unknown cause. One patient (0.3%) had recurrent non-fatal VTE. Only 3 patients (0.8%) died within 7 days, all from definite/possible PE. Patients with RV dysfunction based on our primary definition had the same cumulative incidence of overall mortality and mortality/recurrence of non-fatal VTE than patients without RV dysfunction (Figure 1, Panel A and B). Based on our primary definition, the 30-day overall mortality was 4.2% and 3.5% for patients with and without RV dysfunction, respectively (*P*=0.79), with no difference in definite/possible fatal PEs (2.1% vs. 0.8%; *P*=0.35). Using the presence of ≥1 and ≥2 echocardiographic signs to define RV dysfunction, the overall mortality was 4.3% vs. 1.3% (*P*=0.32) and 4.7% vs. 2.7% (*P*=0.43), respectively.

Association between RV dysfunction and clinical outcomes

RV dysfunction based on our primary definition was not associated with overall mortality (adjusted hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.31-2.58) and the combined outcome of overall mortality/recurrence of non-fatal VTE within 30 days (HR 1.09, 95% CI 0.40-2.98) (Table 3). Using secondary definitions of RV dysfunction, patients with RV dysfunction were somewhat more likely to experience death or death/non-fatal recurrence of VTE than patients without RV dysfunction but the association did not reach statistical significance (Table 3). When we restricted the analysis to the 189 patients (47%) who had TTE within one day of PE diagnosis, the results did not change markedly (results not shown).

DISCUSSION

In our prospective cohort study, we found no significant association between echocardiographic signs of RV dysfunction and clinical outcomes in hemodynamically stable elderly patients with acute PE, irrespective of the definition used. Depending on the definition of RV dysfunction, the prevalence of RV dysfunction varied widely and ranged from 36% using a restrictive (RV/LV end-diastolic diameter ratio >0.9 or RV hypokinesis) to 81% using a broader definition (presence of ≥1 echocardiographic sign). Our findings are consistent with results from prior studies in which the prevalence of echocardiographic RV dysfunction varied greatly from 20% to 68% in hemodynamically stable patients with PE [20, 21]. This substantial heterogeneity in the prevalence has been attributed to the lack of standardization of criteria used to define RV dysfunction and differences in patient characteristics [22]. Moreover, inter-observer reliability of echocardiographic signs of RV dysfunction in hemodynamically stable patients with PE appears to be heterogenous, the agreement between cardiologists varying from fair (κ=0.45) for RV end-diastolic diameter measurement to good for RV hypokinesis (κ=0.70) [23]. A future effort to establish more standardized, reliable criteria of RV function is needed.

In contrast to the majority of studies enrolling younger hemodynamically stable patients with PE [13, 15, 20, 21, 24-30], we did not find a relationship between echocardiographic RV dysfunction and short-term clinical outcomes in our sample of elderly patients. In particular, the specific set of echocardiographic criteria recommended by the American Heart Association (presence of RV/LV end-diastolic diameter ratio >0.9 or RV hypokinesis) was not associated with adverse clinical events. There are several potential explanations for our results. First, only 33% of patients who died during follow-up died from definite/possible PE, indicating that short-term prognosis of elderly patients with acute PE may be more often driven by

comorbidities than by PE-related RV dysfunction. RV dysfunction may also reflect cardiac and pulmonary diseases rather than severity of PE in the elderly [31, 32]. Mortality from definite/possible PE did not differ by RV function in our study.

Second, patients with RV dysfunction were more likely to be admitted to the intensive care unit and to receive fibrinolysis than patients without RV dysfunction, which may have improved an otherwise poor prognosis. However, this scenario seems unlikely in light of the results of the PEITHO trial [33]. While fibrinolysis reduced the risk of decompensation in hemodynamically stable patients with PE who had RV dysfunction and elevated troponin in this trial, overall mortality did not differ, and the risk-benefit ratio of fibrinolysis was worse in patients aged >75 years [34]. Finally, although TTEs were performed according to a standardized protocol, readings were not centrally adjudicated and we have no information about reliability and technical quality of the exams. Although this may be a limitation, the quality of our TTEs is likely to be representative of the real world situation in many hospitals.

In a scientific statement, the American Heart Association recommends fibrinolysis as a treatment option for hemodynamically stable patients with PE who have evidence of moderate to severe RV strain [3]. According to the European Society of Cardiology, patients with stable PE who have both signs of RV dysfunction on TTE and elevated troponin should be closely monitored for clinical deterioration [4]. Our findings do not support the use of TTE in the risk stratification of elderly patients with PE, at least not as a stand-alone risk assessment tool. In a prior study, the use of TTE to risk-stratify patients with PE resulted in higher care levels and more advanced treatments but did not improve outcomes [6].

Our study has several potential limitations. First, we excluded 42% of patients, mostly, because TTE was not available within three days of PE diagnosis. However, excluded patients did not appear to be more severely ill or to have more adverse

outcomes than analyzed patients, making a selection bias unlikely. Second, because PE-related RV dysfunction may be transient and only about half of patients had TTE within one day of PE diagnosis, we may have not captured all patients with initial RV dysfunction. However, when restricting our analysis to patients who had TTE within one day of PE diagnosis, the results did not change. Third, we did not evaluate hemodynamic (PE-related) decompensation, we only collected information regarding PE-related processes of care (e.g., fibrinolysis, intensive care unit admission, administration of catecholamines, and cardiopulmonary resuscitation). However, managing physicians were not blinded to RV function and the utilization of these treatments may have been partially influenced by managing physicians' knowledge of patients' RV function. Thus, the use of these treatments may at least partially reflect guideline or expert recommendations and not the occurrence of hemodynamic decompensation. Fourth, as a predefined ancillary study within the SWITCO65+ prospective cohort, our study was not powered to detect mortality differences between patients with and without RV dysfunction. Specifically, there were not enough PE-related deaths to examine the association between RV dysfunction and PE-related mortality. Finally, our results may not be generalizable to more novel echocardiographic signs that were not examined in our study (e.g., tricuspid annular plane systolic excursion [TAPSE]) [35].

In conclusion, the prevalence of echocardiographic RV dysfunction varies widely based on the criteria used to define RV dysfunction in elderly, hemodynamically stable patients with acute PE. We did not find an association between RV dysfunction and short-term clinical outcomes. Our results do not support TTE as a stand-alone risk stratification tool in the elderly with acute PE.

Conflict of interest statement

The authors have no conflict of interest.

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FIGURE LEGENDS

Figure 1

Panel A. Kaplan-Meier estimates of overall mortality by RV function*

The cumulative incidence of overall mortality at 30 days was 4.2% for patients with RV dysfunction vs. 3.5% for patients without RV dysfunction (*P*=0.728) by the log-rank test).

Panel B. Kaplan-Meier estimates of overall mortality or recurrence of non-fatal venous thromboembolism by RV function*

The cumulative incidence of the combined outcome of overall mortality and recurrence of non-fatal venous thromboembolism at 30 days was 4.9% for patients with RV dysfunction vs. 3.5% for patients without RV dysfunction (*P*=0.501) by the log-rank test).

Abbreviations: RV= right ventricular.

*RV dysfunction was defined as the presence of a RV/left ventricular end-diastolic diameter ratio >0.9 or a right ventricular hypokinesis on transthoracic echocardiography.

Table 1. Patient baseline characteristics by echocardiographic RV function

	RV dysfunction* (N=143)	No RV dysfunction (N=257)	*P*-value
	n (%) or median (IQR)†		
Age, years	75.0 (70.0-84.0)	74.0 (69.0-80.0)	0.041
Male gender	78 (55)	147 (57)	0.674
Active cancer‡	17 (12)	49 (19)	0.069
Heart failure§	21 (15)	25 (10)	0.144
Chronic lung disease‖	19 (13)	38 (15)	0.766
Prior history of VTE	49 (34)	62 (24)	0.036
Unprovoked index PE¶	114 (80)	177 (69)	0.020
Localization of PE#			
Central	62 (43)	73 (28)	0.003
Lobar	73 (51)	98 (38)	0.015
Segmental	93 (65)	179 (70)	0.372
Subsegmental	41 (29)	107 (42)	0.013
Isolated subsegmental	5 (3)	28 (11)	0.013
Unknown localization	9 (6)	9 (4)	0.214
Altered mental status	6 (4)	11 (4)	1.000
Heart rate ≥110 beats/minute	27 (19)	23 (9)	0.007
Systolic blood pressure <100 mm Hg	4 (3)	4 (2)	0.464
Temperature <36 C°	11 (8)	26 (10)	0.588
Respiratory rate ≥30 breaths/minute	11 (8)	5 (2)	0.017
Arterial oxygen saturation <90%	31 (22)	28 (11)	0.005
PESI risk class			0.414
I	1 (1)	4 (2)	
II	37 (26)	85 (33)	
III	48 (34)	81 (31)	
IV	35 (24)	60 (23)	
V	22 (15)	27 (11)	
Anemia††	41 (29)	98 (38)	0.062
Serum creatinine >1.5 mg/dl	11 (8)	29 (11)	0.299
Highly sensitive troponin T >0.1 ng/ml	13 (9)	11 (4)	0.082
NT-proBNP >500 pg/ml	91 (64)	93 (36)	<0.001
VKA therapy prior to PE diagnosis	8 (6)	7 (3)	0.173
Initial parenteral anticoagulation			0.048
Low molecular weight heparin	55 (39)	132 (51)	
Unfractionated Heparin	65 (46)	84 (33)	
Fondaparinux	21 (15)	35 (14)	
No parenteral anticoagulation	2 (1)	6 (2)	
Subsequent VKA therapy	133 (93)	231 (90)	0.363

Continued

Continued

	RV dysfunction* (N=143)	No RV dysfunction (N=257)	*P*-value
	n (%) or median (IQR)†		
Use of inferior vena cava filter	2 (1)	1 (1)	0.292
Admission to intensive care unit	25 (18)	22 (9)	0.010
Use of intravenous catecholamines‡‡	3 (2)	4 (2)	0.704
Cardiopulmonary resuscitation	3 (2)	0 (0)	0.045
Fibrinolysis§§	11 (8)	4 (2)	0.004
Thromboembolectomy‖‖	0 (0)	1 (1)	1.000

Abbreviations: RV= right ventricular; IQR= interquartile range; VTE= venous thromboembolism. PESI= Pulmonary Embolism Severity Index; PE= pulmonary embolism; VKA= vitamin K antagonist.

*RV/left ventricular end-diastolic diameter ratio >0.9 or RV hypokinesis.

†Data were missing for heart rate (1%), systolic blood pressure (1%), temperature (3%), respiratory rate (21%), arterial oxygen saturation (5%), anemia (1%), creatinine (2%), hsTNT (11%), and NT-proBNP (11%).

‡Cancer requiring surgery, chemotherapy, radiotherapy, or palliative care during the last 3 months.

§Acute heart failure NYHA class II-IV during the last 3 months, history of systolic/diastolic heart failure, left/right heart failure, forward/backward heart failure, or left ventricular ejection fraction of <40%.

‖Chronic obstructive pulmonary disease, active asthma, lung fibrosis, cystic fibrosis, or bronchiectasies.

#Absence of major surgery, estrogen therapy, or immobilization (fracture or cast of the lower extremity, bed rest >72 hours, or voyage in sitting position for >6 hours) during the last 3 months.

#Multiple localizations per patient were possible.

††Hemoglobin <130 g/l for men and <120 g/l for women.

‡‡Dopamin, dobutamin, adrenalin, noradrenalin, or vasopressin.

§§Systemic or catheter-based fibrinolysis.

‖‖Catheter-based or surgical thromboembolectomy.

Table 2. Prevalence of echocardiographic signs of RV dysfunction (N=400)

Echocardiographic sign	n (%)*
RV/LV end-diastolic diameter ratio >0.9	124 (31)
RV hypokinesis	58 (15)
Paradoxical septal motion	82 (21)
Reduced inspiratory collapse of the inferior vena cava	109 (27)
Pulmonary acceleration time ≤100 ms	216 (54)
RV/right atrial gradient ≥30 mm Hg	193 (48)
Presence of RV/LV end-diastolic diameter ratio >0.9 or RV hypokinesis	143 (36)
Presence of ≥1 sign of RV dysfunction	324 (81)
Presence of ≥2 signs of RV dysfunction	213 (53)

Abbreviations: RV= right ventricular; LV= left ventricular.

*6% of patients had missing values for RV/LV ratio, 2% for RV hypokinesis, 3% for paradoxical septal motion, 11% for inspiratory collapse of the inferior vena cava, 22% for pulmonary acceleration time, and 23% for RV/right atrial gradient.

Table 3. Association between echocardiographic RV dysfunction and clinical outcomes within 30 days

	Adjusted hazard ratio* (95% confidence interval)
RV/LV ratio >0.9 or RV hypokinesis	
Overall mortality	0.90 (0.31-2.58)
Overall mortality or recurrence of non-fatal VTE	1.09 (0.40-2.98)
Presence of ≥1 sign of RV dysfunction†	
Overall mortality	2.22 (0.28-17.42)
Overall mortality or recurrence of non-fatal VTE	2.52 (0.32-19.57)
Presence of ≥2 signs of RV dysfunction†	
Overall mortality	1.43 (0.48-4.20)
Overall mortality or recurrence of non-fatal VTE	1.60 (0.55-4.64)

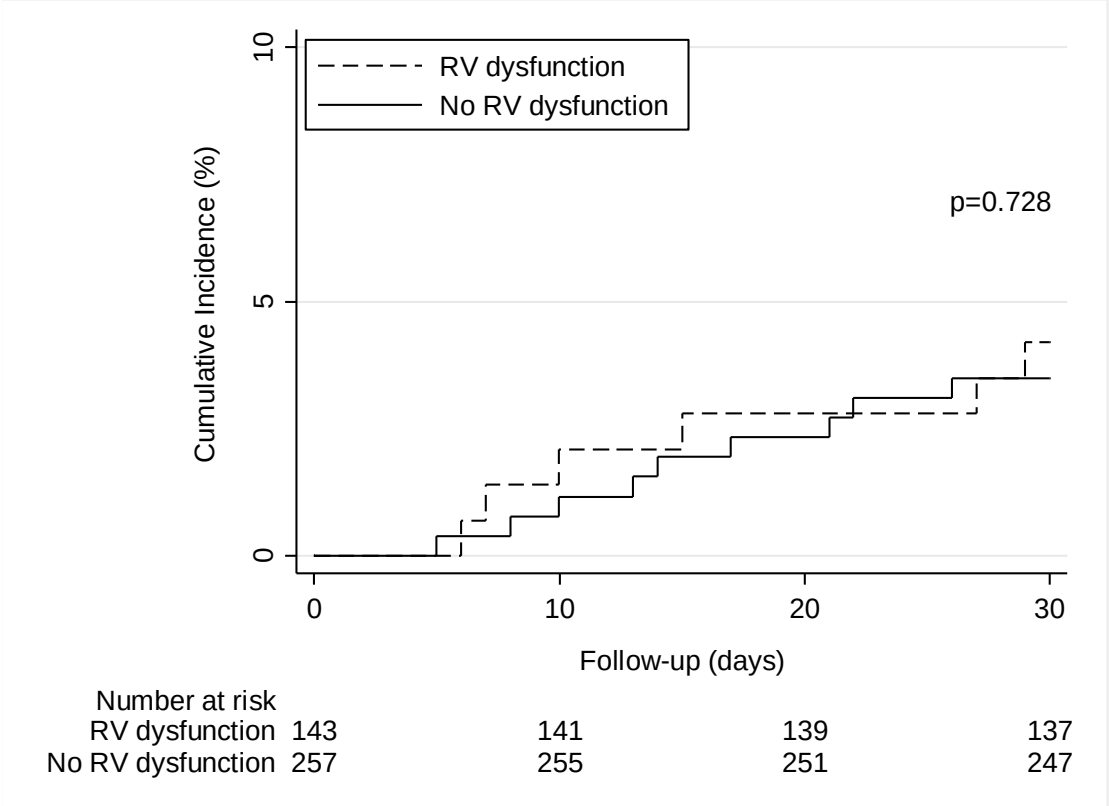
Abbreviations: RV= right ventricular, LV= left ventricular, VTE= venous thromboembolism.

*Adjusted for Pulmonary Embolism (PE) Severity Index risk score and hsTnT >0.1 ng/ml.

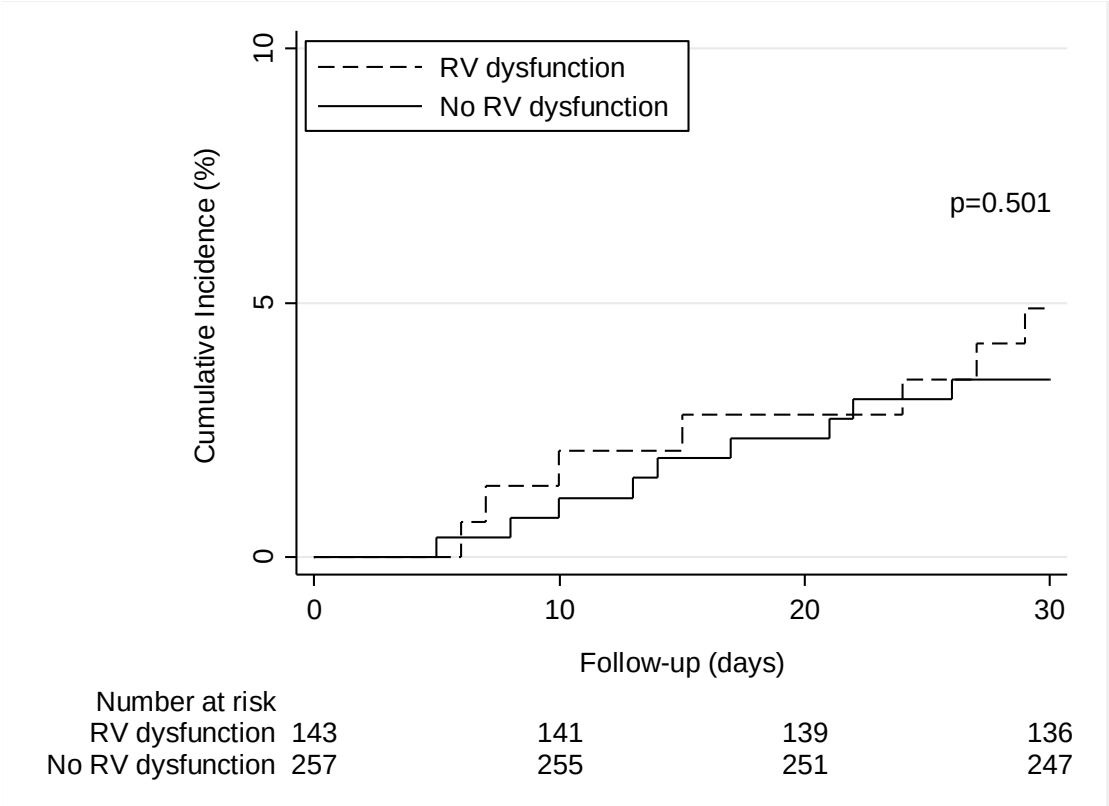
†RV/LV end-diastolic diameter ratio >0.9 in the apical four chamber view, RV hypokinesis, paradoxical septal motion, decreased or absent inspiratory collapse of the inferior vena cava, decrease in pulmonary acceleration time in the parasternal short axis view (≤100 ms), or increase in RV/right atrial gradient in the apical four chamber or parasternal short axis view (≥30 mm Hg).

Figure.

A.


RV dysfunction
No RV dysfunction
p=0.728
Cumulative Incidence (%)
0
5
10
0
10
20
30
Follow-up (days)
Number at risk
RV dysfunction 143 141 139 137
No RV dysfunction 257 255 251 247

B.


RV dysfunction
No RV dysfunction
p=0.501
Cumulative Incidence (%)
0
5
10
0
10
20
30
Follow-up (days)
Number at risk
RV dysfunction 143 141 139 136
No RV dysfunction 257 255 251 247